The Impact of Biomarker Screening and Cascade Genetic Testing on the Cost-Effectiveness of MODY Genetic Testing

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OBJECTIVE

In the U.S., genetic testing for maturity-onset diabetes of the young (MODY) is frequently delayed because of difficulty with insurance coverage. Understanding the economic implications of clinical genetic testing is imperative to advance precision medicine for diabetes. The objective of this article is to assess the cost-effectiveness of genetic testing, preceded by biomarker screening and followed by cascade genetic testing of first-degree relatives, for subtypes of MODY in U.S. pediatric patients with diabetes.

RESEARCH DESIGN AND METHODS

We used simulation models of distinct forms of diabetes to forecast the clinical and economic consequences of a systematic genetic testing strategy compared with usual care over a 30-year time horizon. In the genetic testing arm, patients with MODY received treatment changes (sulfonylureas for HNF1A- and HNF4A-MODY associated with a 1.0% reduction in HbA_{1c}; no treatment for GCK-MODY). Study outcomes included costs, life expectancy (LE), and quality-adjusted life years (QALY).

RESULTS

The strategy of biomarker screening and genetic testing was cost-saving as it increased average quality of life (+0.0052 QALY) and decreased costs (−$191) per simulated patient relative to the control arm. Adding cascade genetic testing increased quality-of-life benefits (+0.0081 QALY) and lowered costs further (−$735).

CONCLUSIONS

A combined strategy of biomarker screening and genetic testing for MODY in the U.S. pediatric diabetes population is cost-saving compared with usual care, and the addition of cascade genetic testing accentuates the strategy's benefits. Widespread implementation of this strategy could improve the lives of patients with MODY while saving the health system money, illustrating the potential population health benefits of personalized medicine.

Maturity-onset diabetes of the young (MODY) is an autosomal-dominant, noninsulin-dependent form of diabetes accounting for 0.8–2.5% of all diabetes cases (1–4). MODY is frequently misdiagnosed and treated as either type 1 or type 2 diabetes (5). Misdiagnosis has significant implications for both the cost and efficacy of treatment

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for MODY patients with heterozygous mutations in the *HNF1A*, *HNF4A*, and *GCK* genes, which together account for more than 90% of MODY cases (6). Sulfonylureas are first-line therapy for patients with HNF1A- and HNF4A-MODY, resulting in decreased treatment costs and improved glycemic control relative to metformin and/or insulin treatment (7–10). Patients with GCK-MODY have stable, mild hyperglycemia and do not require treatment outside of pregnancy (11). Thus, a proper MODY diagnosis can lower treatment costs, reduce the burden of diabetes care, and improve the quality of life for individuals with MODY. Despite this, patients frequently encounter barriers to insurance coverage for genetic testing, resulting in substantial delays between a diabetes diagnosis and an accurate genetic diagnosis of MODY (12). Within the University of Chicago National Monogenic Diabetes Registry, 73% of individuals with MODY due to *HNF1A*, *HNF4A*, or *GCK* mutations were diagnosed as part of a research study, rather than by commercial-based genetic testing, highlighting barriers to clinical implementation of MODY genetic testing.

The first cost-effectiveness analysis (CEA) of MODY genetic testing, which was carried out in a U.S. population of young adults with type 2 diabetes, compared routine genetic testing via Sanger sequencing for mutations in *HNF1A*, *HNF4A*, and *GCK* to no genetic testing. This testing strategy was found to be prohibitively expensive to implement across the entire study population. The incremental cost-effectiveness ratio (ICER) was $205,000 (ICER = $/quality-adjusted life years [QALY]), exceeding the typical threshold for cost-effectiveness of $50,000/QALY (13). However, sensitivity analyses showed that the strategy would become cost-effective if MODY prevalence could be increased to 6% in the tested population. Several studies have explored biomarker screening, including negativity for islet cell autoantibodies and positivity for C-peptide, to identify patients more likely to test positive for MODY (1,4,14,15). A CEA of MODY genetic testing based in Singapore found that the addition of biomarker screening prior to genetic testing lowered costs associated with screening but still resulted in an ICER above $50,000/QALY ($93,663) (16). More recently, a CEA applying massively parallel sequencing (MPS) to an Australian pediatric population of patients with presumed type 1 diabetes was found to be a cost-saving measure when compared with testing based on clinical suspicion (17).

Given the heterogeneity of study populations, testing strategies, and findings of prior CEAs, we sought to conduct a comprehensive CEA of a strategy of genetic testing for MODY, preceded by biomarker screening and followed by testing first-degree relatives of probands (cascade genetic testing), in a U.S. pediatric population with clinically diagnosed type 1 and type 2 diabetes. To date, no CEAs of MODY genetic testing have accounted for cascade genetic testing. Since relatives can be tested at a substantially lower cost compared with the index case, cascade testing has been shown to greatly enhance the cost-effectiveness of genetic testing when applied to other autosomal-dominant conditions, such as Lynch syndrome and familial hypercholesterolemia (18,19).

RESEARCH DESIGN AND METHODS

Study Framework

We used a series of computer simulation models for HNF1A-/HNF4A-MODY, GCK-MODY, type 1 diabetes, and type 2 diabetes to compare a policy of applying universal biomarker screening to individuals with diabetes between the ages of 10 and 20 years followed by genetic testing for patients with negativity for islet cell autoantibodies and positivity for C-peptide (testing arm) to usual care (control arm) (Fig. 1). The analysis was conducted from a health care sector perspective over a 30-year time horizon in the base case. Analyses were also conducted over 10-year and lifetime time horizons. Future costs and QALYs were discounted at an annual rate of 3%.

Population Characteristics

Simulated patient cohort characteristics were derived from the SEARCH for Diabetes in Youth (SEARCH) study, the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial, and other studies focused on young populations in the U.S. with additional data from the Centers for Disease Control and Prevention (Supplementary Table 1). Since our study only considered HNF1A-, HNF4A-, and GCK-MODY, the prevalence of type 1 diabetes, type 2 diabetes, and these MODY types derived from SEARCH was normalized to 100% to reflect the population assessed for monogenic diabetes by SEARCH. This slightly inflated the percentage of patients with type 1 or type 2 diabetes (98.8% in our model compared with 97.5% reported in SEARCH) (4,20).

Biomarker Screening and Genetic Testing

The vast majority of MODY patients are negative for islet autoantibodies and positive for C-peptide (14,15). In this study, biomarker screening of GAD65 and IA-2 autoantibodies and plasma fasting C-peptide was applied to the entire testing arm cohort. All autoantibody-negative and C-peptide–positive patients, including an assumed 100% of MODY patients, were modeled to undergo simultaneous genetic testing for heterozygous mutations in *GCK*, *HNF1A*, and *HNF4A* (Fig. 1). Genetic testing was modeled as 100% sensitive and 100% specific.

Treatment Changes with Genetic Diagnosis

Treatment profiles for MODY patients in the control arm were based on treatments MODY patients in the SEARCH study were receiving before researchers identified them as positive for MODY (4) (Fig. 1). These treatment profiles include some patients who were being treated appropriately for their genetic subtype based on clinical suspicion. In the testing arm, patients diagnosed with HNF1A-/HNF4A-MODY were switched to sulfonylurea pills. With sulfonylureas, we assumed patients would experience a 1% reduction in HbA_{1c} during the 1st year. To reflect the reported failure of sulfonylureas over time, we modeled a 20% failure chance within the 1st decade of treatment, with an additional 10% failure chance in both the 2nd and 3rd decades of treatment. Sulfonylurea failure was modeled with an assumed HbA_{1c} increase of 0.3%. When sulfonylurea treatment failed, insulin, metformin, or dipeptidyl peptidase 4 inhibitors were added to the treatment regimen based on proportions reported by Bacon et al. (21). Patients with GCK-MODY were taken off all medications in the testing arm with no impact on HbA_{1c} because

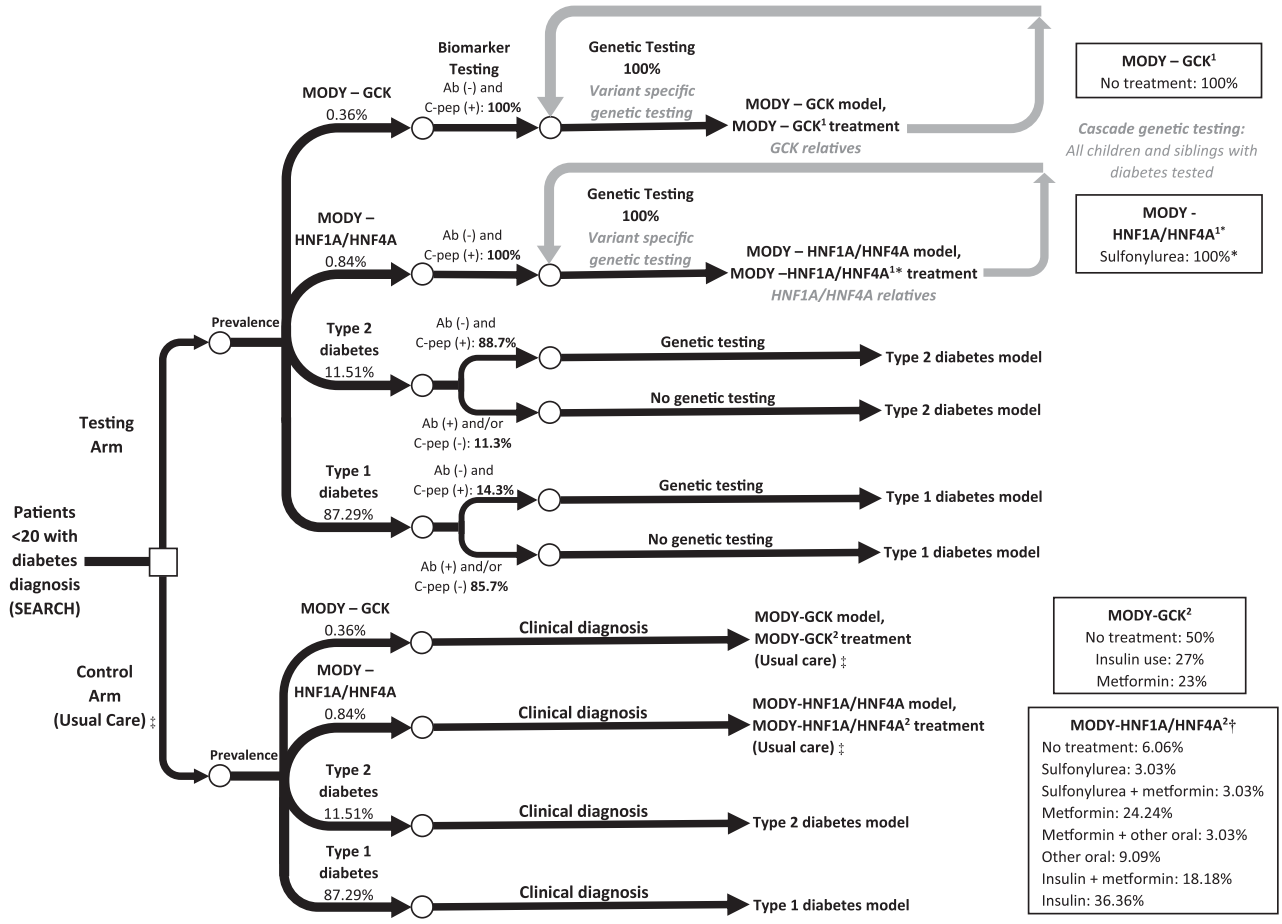

Figure 1—Decision tree for biomarker screening, genetic testing, and cascade genetic testing in patients with diabetes. Prevalence data for all diabetes types were derived from SEARCH studies (4,20). The autoantibody and C-peptide data for type 1 diabetes and type 2 diabetes patients were drawn from another SEARCH study (42). *Sulfonylurea failure rates for HNF1A/HNF4A: 20% in the 1st decade, 10% in the 2nd decade, 10% in the 3rd decade; new treatment: 62.5% sulfonylurea + insulin, 25% sulfonylurea + metformin, 12.5% sulfonylurea + dipeptidyl peptidase 4 inhibitor (21). †Several assumptions were made regarding the proportion of patients with HNF1A/HNF4A on dual therapy to best agree with the treatment profile reported by Pihoker et al. (4). ‡The control arm refers to the current status quo (usual care). The usual care treatment profiles for patients with MODY refers to the treatments they were receiving before being identified as MODY positive by the Pihoker et al. (4) research team. Thus, a small number of patients were already correctly diagnosed and treated based on clinical suspicion. [1]Treatments in the testing arm. [2]Treatments in the control arm. Ab, islet cell autoantibody; C-pep, C-peptide.

GCK-MODY does not require pharmacologic therapy outside of pregnancy and discontinuation of therapy does not alter HbA_{1c} (22,23).

Cascade Testing

The numbers of relatives with diabetes, prediabetes, or hyperglycemia per proband were estimated from the University of Chicago National Monogenic Diabetes Registry (24). Because the simulation models were constructed for patients under 20 years of age, we restricted analysis to children and siblings of probands. Using registry data, we characterized the distribution of the number of relatives of HNF1A-, HNF4A- and GCK-MODY patients. In the simulation, relatives were assigned similar baseline characteristics as their respective proband sibling. Given MODY's autosomal-dominant inheritance pattern, 50% of these relatives were assumed to be positive for MODY, and the other 50% were assumed to have either type 1 or type 2 diabetes in the appropriate population proportions. This 50% assumption is conservative given the high likelihood of MODY positivity in these relatives with diabetes.

Simulation Models

We developed separate simulation models to account for the costs and complications of HNF1A-/HNF4A-MODY, GCK-MODY, type 1 diabetes, and type 2 diabetes. All four models were built using R, version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). All four included "other cause" mortality not associated with diabetes disease processes (25,26). We used a modified Sheffield Type 1 Diabetes Policy Model to model type 1 diabetes complication rates (27,28). We used risk equations from the UK Prospective Diabetes Study Outcomes Model 2 (UKPDS OM2) to model type 2 diabetes complication rates (29). HNF1A-/HNF4A-MODY patients are more similar to patients with type 1 diabetes than those with type 2 diabetes in regard to diagnosis age, insulin sensitivity, and obesity rates. Thus, with no existing complications model available for HNF1A-/HNF4A-MODY, we used the Sheffield model to predict complications in this population.

Patients with GCK-MODY have similar rates of microvascular and macrovascular complications compared with the general population (11,30). Thus, we

used a 30-year risk model for cardiovascular (CV) disease developed from the Framingham Offspring cohort to model CV risk in GCK-MODY patients (31). This model was applied once patients reached the age of 20 years to determine their annual chance of CV events (CV death, myocardial infarction, or fatal/nonfatal stroke). The probability of death from various CV events was derived from national estimates from the American Heart Association (32). After age 50 years in the lifetime model, we used risk equations for atherosclerotic cardiovascular disease (ASCVD) from the 2013 American College of Cardiology and American Heart Association guideline on the assessment of CV risk (33) (Supplementary Table 2).

Each simulated patient progressed annually through the various complication modules until either the end of the 30-year simulation or a death event. For each diabetes model, 500 patients were simulated with 1,000 iterations. Models were run independently, and then 200 cohorts of 50,000 patients were sampled based on appropriate population proportions for each diabetes type (Fig. 1). Outcomes from these cohorts were bootstrapped to produce outcome means and CIs.

Costs

All costs were expressed in 2018 U.S. dollars. Cost of biomarker screening was set at $41.75 based on estimates for C-peptide, GAD65 antibody, and IA-2 antibody testing from a clinical laboratory (Commercial Reference Laboratory Pricing). No additional outpatient visit was included in the biomarker screening price because biomarker screening was assumed to be applied during routine outpatient visits. The cost of simultaneously sequencing *GCK*, *HNF1A*, and *HNF4A*, including an additional outpatient visit, was set at $3,732.96 per individual. Since the specific genetic variant is determined during proband testing, the cost of cascade testing of the proband's relatives, including an additional outpatient visit, was $612.96 (Commercial Reference Laboratory Pricing; Bureau of Labor Statistics). Oral medication costs and per-unit insulin costs were based on values reported in prior CEAs (25,28) (Supplementary Table 3). Insulin treatment costs included self-monitoring costs and assumed fixed proportions of patients treated with different insulin treatment strategies (Supplementary Table 4). We also accounted for diabetes complication costs (28) (Supplementary Table 5).

Quality-of-Life Effects

Baseline health utility values for pediatric patients with type 1 diabetes (0.90) and type 2 diabetes (0.92) were based on the average of the health utilities reported both by patients and by parent proxy (34,35) (Supplementary Table 5). Since insulin and oral medications have different health utility multipliers (0.966 vs. 0.977) (25), we modified baseline utility for HNF1A-/HNF4A-MODY patients in the control arm based on the proportion of patients on oral meds versus insulin and modified the testing arm utility assuming 100% adoption of oral meds. Since patients with GCK-MODY do not have an increased risk of complications compared with the nondiabetic population, we modeled a baseline health utility of 1.00 for GCK-MODY patients in the testing arm. GCK-MODY patients in the control arm had a lower baseline health utility value (0.986) due to medication effects. Utility changes associated with complications in the HNF1A-/HNF4A-MODY and type 1 diabetes models were similar to those reported elsewhere and were applied in a multiplicative fashion (28). These utility changes were similarly applied to CV outcomes in the GCK-MODY model. Utility changes associated with complications for type 2 diabetes patients were similar to those reported elsewhere (25).

Updating Characteristics

Since the starting populations were young and risk factors change with age, we updated relevant risk factors at age 20 years for each of the four population groups (Supplementary Table 1). We based updated characteristics for HNF1A-/HNF4A-MODY and type 1 diabetes on a study that compared complication rates in HNF1A-MODY and type 1 diabetes adult populations (21). GCK-MODY characteristics were updated to those reported by a study of complication rates in GCK adults (30). Type 2 diabetes characteristics were updated to those reported in the UKPDS OM2 publication (29). Further, since insulin dosing is based on body weight, we accounted for developmental changes in body weight and the accompanying changes in insulin costs. Using the BMI *z* scores present in the baseline populations, we defined approximate weight percentiles that were tracked over time for each diabetes type using a Centers for Disease Control and Prevention growth chart (36) (Supplementary Table 6). At age 20 years, weight was assumed to stabilize for the remainder of the simulation.

Study Outcomes and Sensitivity Analyses

The study outcomes included costs, life expectancy (LE), and QALYs. The ICER was calculated as the ratio of the difference in costs and the difference in QALYs between the testing and control arms. The models were first run with biomarker screening and genetic testing only, and then with the addition of cascade testing to determine the effect of each intervention on outcomes. One-way sensitivity analyses were performed on several parameters to determine their effect on costs and QALYs, and the results were converted into net monetary benefit (NMB) assuming a willingness-to-pay (WTP) threshold of $50,000 per QALY. NMB was calculated by multiplying the WTP threshold by incremental QALY changes and then subtracting incremental cost changes for the various interventions. All data analyses were performed in R.

RESULTS

Biomarker Screening + Genetic Testing Outcomes

All outcomes are reported as mean values per patient over the 30-year time horizon. In the base case for the overall population, biomarker screening and genetic testing for MODY was associated with a slight increase in LE (+0.0030 years) and quality of life (+0.0052 QALY) in the testing arm relative to the control arm. The testing arm cost decreased (−$191) relative to the control arm. The strategy was thus cost-saving. Since costs decreased and quality of life increased, the testing arm dominated the control arm (Table 1).

The subgroup analysis (Table 2) illuminates considerable cost and quality-of-life differences between the different diabetes types. Costs for patients with type 1 and type 2 diabetes increased slightly (+$576 and +$3,353, respectively) because of biomarker screening costs and genetic testing in a portion of the population. Since there were no

Table 1—Total cost, LE, QALY, and ICER outputs

Outcomes	Control	Testing	Difference [95% CI]
Biomarker + genetic testing			
Cost ($)	300,091.42	299,900.57	−190.84 [−209.83 to −171.23]
LE (years)	27.9299	27.9329	+0.0030 [0.0027–0.0034]
QALY	16.3556	16.3608	+0.0052 [0.0050–0.0054]
ICER ($/QALY)	—	—	Dominant
Addition of cascade testing			
Cost ($)	299,419.30	298,684.69	−734.61 [−760.05 to −708.72]
LE (years)	27.9332	27.9382	+0.0050 [0.0046–0.0055]
QALY	16.3619	16.3700	+0.0081 [0.0078–0.0083]
ICER ($/QALY)	—	—	Dominant

Costs, LE, and QALY are expressed as mean amounts per patient over the 30-year time horizon of the study.

treatment changes associated with type 1 and type 2 diabetes modeled in the testing arm, there were no LE or QALY differences associated with these diabetes types. For the HNF1A-/HNF4A-MODY cohort, costs decreased (−$113,547), LE increased (+0.47 years), and quality of life increased (+0.56 QALY) because of changes from insulin treatment to pills and decreased complication rates (Supplementary Table 7) associated with improved glycemic control. Costs for patients with GCK-MODY decreased (−$31,767), and quality of life increased (+0.28 QALY) because of cessation of medications.

Over a 10-year time horizon, the testing arm was associated with a smaller increase in quality of life (+0.0011 QALY) and increased costs per patient (+$547) relative to the control arm (Supplementary Table 8). When the time horizon was extended to patient lifetimes, the testing arm was associated with a larger increase in quality of life (+0.0133 QALY) and a larger decrease in cost (−$603), making the intervention even more cost-saving than the base case.

Cascade Genetic Testing Outcomes

On average, HNF1A-, HNF4A- and GCK-MODY patients had 1.01 relatives with hyperglycemia, prediabetes, or diabetes (Supplementary Table 9). Assuming 50% of relatives to be MODY positive, the application of cascade genetic testing in addition to biomarker screening and proband genetic testing further increased LE (+0.0050 years) and quality of life (+0.0081 QALY) in the testing arm relative to the control arm. Cascade testing also further decreased costs (−$735) per patient. Thus, the application of cascade genetic testing made the intervention even more cost-saving (Table 1).

Table 2—Cost, LE, and QALY outputs for each diabetes type (30-year time horizon)

	Cost ($)	LE (years)	QALY
Type 1 diabetes			
Control	331,958.30	28.03*	16.33*
Testing	332,533.86	28.03*	16.33*
Difference	+575.56	0	0
Type 2 diabetes			
Control	67,708.70	27.31*	16.56*
Testing	71,061.59	27.31*	16.56*
Difference	+3,352.89	0	0
HNF1A-/HNF4A-MODY			
Control	256,056.30	28.12	16.53
Testing	142,508.81	28.59	17.09
Difference	−113,547.49	+0.47	+0.56
GCK-MODY			
Control	37,879.11	29.50	19.61
Testing	6,111.87	29.49	19.89
Difference	−31,767.24	−0.01	+0.28

*The screening strategy was designed such that QALY and LE for patients with type 1 and type 2 diabetes would not change between the two arms. Thus, any random variation due to sampling was averaged out to produce these values.

Sensitivity Analyses

The NMB of the base case analysis, which included biomarker screening and proband genetic testing, was +$450.84 per patient (Fig. 2). Analyses with positive NMBs were considered cost-effective. The only scenario that was not cost-effective was with the assumption of a lower MODY prevalence of 0.8% (NMB = −$4.79; +$185, +0.0036 QALY) (2). Assuming a prevalence of 2.5% accentuated the cost-savings of the screening strategy (NMB = +$1927.99; −$1,363, +0.0113 QALY) (1). Even when increasing biomarker screening costs from $41.75 to $132.25, which includes the cost of a full autoantibody panel (GAD65, IA-2, insulin autoantibody, and zinc transporter 8 [ZnT8] autoantibody) and higher cost estimates from an alternate clinical laboratory, the screening strategy remained cost-saving (NMB = +$265.25; −$0.25, +0.0053 QALY) (Commercial Reference Laboratory Pricing). Sensitivity analyses with higher genetic testing costs, smaller HbA_{1c} benefits, and a higher sulfonylurea failure rate did not substantially alter the overall NMB estimate.

CONCLUSIONS

In this study, a combined strategy of biomarker screening and genetic testing for MODY in the U.S. pediatric population of patients with diabetes was cost-saving. The addition of cascade genetic testing accentuated cost-savings.

In prior CEAs of MODY genetic testing, MODY prevalence in the tested population was the main determinant of cost-effectiveness. In our study, biomarker screening restricted genetic testing to a subpopulation with a high probability of having MODY. The addition of biomarker screening restricted genetic testing to 23.9% of the total U.S. pediatric population with diabetes. Assuming a 1.2% MODY prevalence in the overall diabetes population, about 5% of patients who received genetic tests were MODY positive. Sensitivity analyses revealed the importance of MODY prevalence on the cost-effectiveness of the testing strategy, which produced even more cost-savings (NMB = +$1927.99) assuming a MODY prevalence of 2.5%.

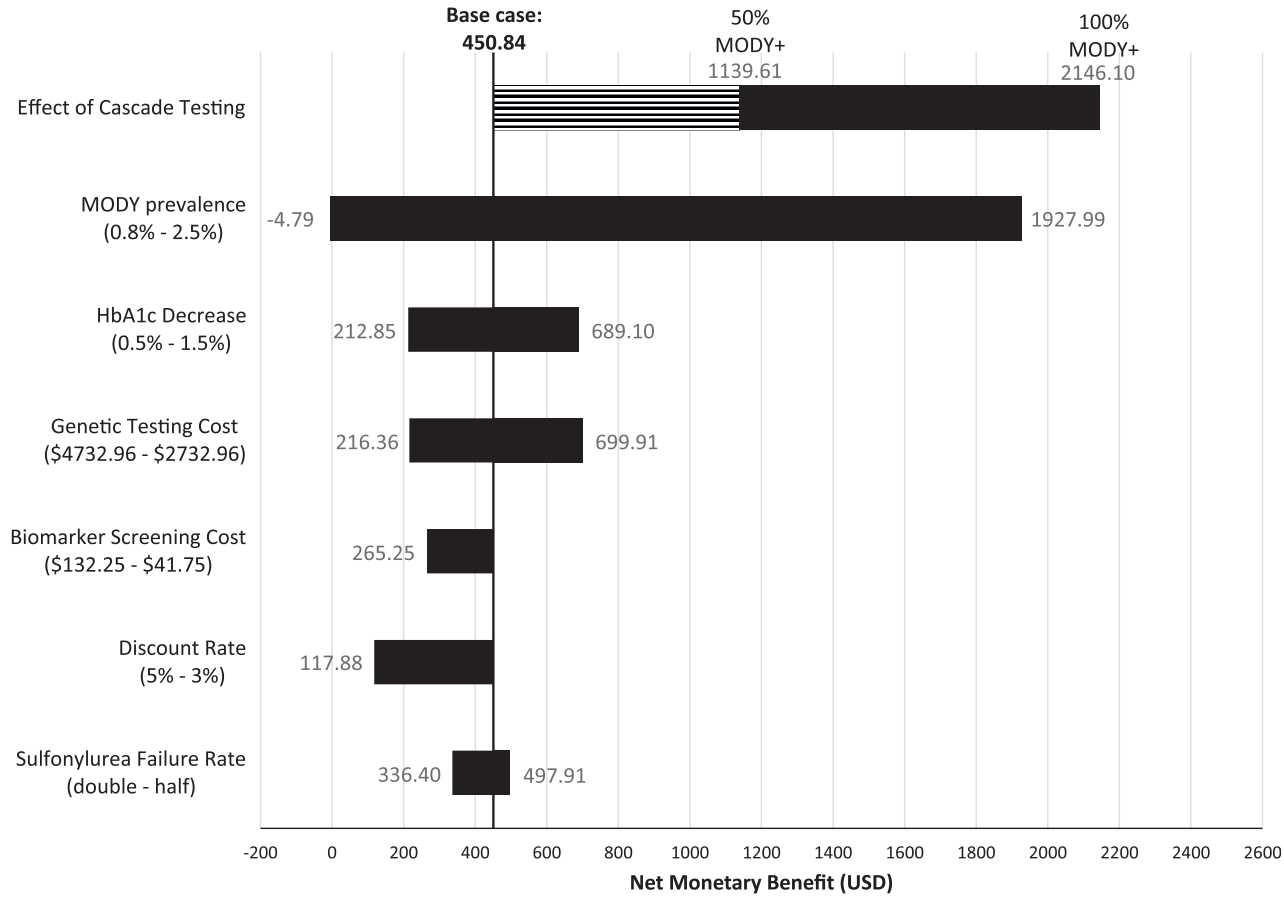

Figure 2—Sensitivity analyses. One-way sensitivity analyses showing the effect on the NMB when varying single parameters between two extremes. All analyses assumed a WTP threshold of $50,000. The NMB for the base case analysis (which includes biomarker screening and proband genetic testing only) was $450.84. All analyses with a positive NMB were considered cost-effective. For the purposes of this sensitivity analysis, cascade testing was applied assuming that 50% or 100% of relatives were MODY-positive (number of relatives assumed shown in Supplementary Table 9). MODY prevalence end points were based on prevalence estimates from the literature (1,2). When adjusting MODY prevalence, the HNF1A/HNF4A:GCK ratio remained constant. HbA_{1c} decrease refers to HbA_{1c} benefit for HNF1A/HNF4A patients when switched to sulfonylurea medication. Biomarker screening rates were based on estimates from two different commercial laboratories. The biomarker screening cost used in the base case ($41.75) includes C-peptide, GAD65, and IA-2 antibodies, whereas the $132.25 screening price includes C-peptide and a full autoantibody panel (insulin, GAD65, IA-2, and ZnT8 autoantibodies). Sulfonylurea failure rates: half = 10% in the 1st decade, 5% in the 2nd and 3rd decades; double = 40% in the 1st decade, 20% in the 2nd and 3rd decades. USD, U.S. dollars.

In our study, the combination of biomarker screening and genetic testing was cost-saving. However, the CEA by Nguyen et al. (16) of a similar testing strategy did not find the strategy cost-effective. Major differences in study design explain the differences between these results. First, our study assumed a HbA_{1c} reduction for patients with HNF1A-/HNF4A-MODY who switched to sulfonylureas. This assumption was based on improvements in glycemic control reported in the literature (21,37,38). Since HbA_{1c} is a predictor of complication rates in the HNF1A-/HNF4A-MODY model, patients in the testing arm developed far fewer complications, which resulted in significantly decreased costs and increased QALYs (Table 2 and Supplementary Table 7). Further, the differences in the results of the two studies can be explained by differences in the prevalence of type 1 and type 2 diabetes by age groups (20,39). Given the high prevalence of type 1 diabetes in our pediatric study population, using autoantibody and C-peptide biomarkers to exclude most individuals with type 1 diabetes and some individuals with type 2 diabetes from genetic testing led to the exclusion of 76.1% of the starting population (Fig. 1). In the Nguyen et al. study, which was conducted in an adult population, only 6.8% of patients with assumed type 1 diabetes based on autoantibody and C-peptide screening were excluded from genetic testing. A further 51.7% of patients with age at diagnosis and BMI consistent with a type 2 diabetes etiology were also excluded. This left 41.5% of the adult population to be tested compared with 23.9% of the pediatric population in our model.

Cascade testing assumptions in our study were conservative. First, because we used pediatric data to build our diabetes models, we only considered cascade testing in siblings and offspring of probands. Not accounting for first-degree relatives >20 years may have undervalued our CEA. CEA studies for other autosomal-dominant conditions have modeled a higher number of relatives assumed to undergo genetic testing per proband, with ranges from 1.1 to 8 (18). In our study, we limited cascade genetic testing to people with abnormal

glycemia, to reflect the data derived from the University of Chicago National Monogenic Diabetes Registry. Thus, fewer relatives were tested per proband (1.01) (Supplementary Table 9). Further, we assumed that only 50% of relatives would test positive for MODY. This assumption would be appropriate for many autosomal-dominant conditions using genetic testing for a presymptomatic diagnosis. However, in our study, only relatives with known hyperglycemia, prediabetes, or diabetes diagnoses were tested. Diabetes in these high-risk relatives would be more than 50% likely to be because of the MODY mutations in their related probands. Thus, assuming 50% of relatives testing positive is a conservative assumption, and even so, the addition of cascade testing further enhanced cost-savings.

Like our present study in a pediatric population, a recent study applying routine MPS screening to an Australian type 1 diabetes pediatric population was cost-saving (17). The advanced sequencing approach was a factor in achieving this result with routine screening. However, a limitation of the Australian study is that MPS of all known MODY genes is not yet commercially available in many laboratories, and it is unclear how expensive commercial pricing for such MPS will be compared with single-gene and MODY panels that are currently available. Our study extends these findings to both pediatric type 1 and type 2 diabetes and shows cost-savings even with lower MODY prevalence (1.2% compared with 2.1%) and less-efficient sequencing. Taken together, these studies argue strongly that genetic testing for MODY should be carried out in all cases of pediatric diabetes to ensure timely, accurate diagnosis. In adult diabetes populations, enhancing cost-effectiveness through the combination of biomarker screening, MPS platforms, and cascade genetic testing could perhaps make a MODY genetic testing strategy cost-effective, but formal investigation into this question is required.

Using the SEARCH study, which is a multicenter, population-based study of diabetes in U.S. youth, to inform baseline characteristics and treatment profiles was a strength of this study. Doing so allowed for modeling of real-world scenarios that would likely occur if MODY genetic testing was widely implemented into clinical practice. First, some misdiagnosed patients with MODY were nevertheless receiving appropriate therapy in the control arm. For example, 50% of those with GCK-MODY were already not on medication (Fig. 1). Genetic diagnoses in such individuals would serve to clarify their diabetes etiology but would not impact treatment costs. Thus, the genetic testing strategy was not overvalued by assuming 100% treatment rates in the control arm. Second, a portion of the population was missing antibody data and only GAD65 and IA-2 antibodies were assessed in the SEARCH study, which increased the number of patients with type 1 diabetes undergoing genetic testing and, therefore, biased against the testing strategy in our study. Sensitivity analysis (Fig. 2) showed that even with the application of a more expensive panel for four anti-islet cell antibodies (GAD65, IA-2, insulin autoantibody, and ZnT8), the strategy was still cost-saving (NMB = +$262.25). This result likely underestimates cost-savings because testing all four anti-islet cell antibodies would serve to further enrich a MODY-positive population. The decision to use commercial cost estimates was also a significant strength of our model. These current clinical cost estimates accurately represent U.S. health system costs for these tests and can be used to aid decisions about genetic testing coverage.

There are important limitations of these simulation models. First, the studies referenced for the baseline characteristics and treatment responses of MODY patients had relatively small sample sizes, reflecting the poor ascertainment of MODY cases nationwide (4,21,30). Secondly, since no model currently exists to describe MODY complication rates, outcome models that are not validated for MODY were used. The Sheffield type 1 diabetes model used to simulate HNF1A-/HNF4A-MODY patients, for example, does not perfectly describe the HNF1A- and HNF4A-MODY disease processes. As a result, this study may have under- or overestimated complication rates in both the control and testing arms for these patients. Future studies focused on complication incidence for MODY patients would be necessary to properly evaluate the accuracy of this study. Further, both the Sheffield model and the UKPDS OM2 model were developed to describe older adult populations, and it is unclear how accurate they are when applied to children and younger adults. Next, although we used data from the SEARCH study's multiethnic population, the models only allowed for "white" and "black" as race inputs. Thus, the simulation did not accurately describe other race groups, particularly Hispanic and Asian/Pacific Islander cohorts, that represented non-negligible proportions of participants in the SEARCH study (4). Diabetes and CV risk models (such as the Framingham 30-year and ASCVD models used in the GCK model) developed using more race categories are required for this simulation to be truly nationally representative.

Lastly, conducting this CEA study from the health care sector perspective limits generalizability of the results to the broader context of society. We chose this perspective to allow comparisons to past CEAs of monogenic diabetes, which have been conducted from either a health care perspective (13,17) or a payer's perspective (16), with the exception of the CEA by Greeley et al. (40) of genetic testing in congenital diabetes, which took patient caretaker time costs into account. We suspect that accounting for these and other societal costs including patient time, productivity, transportation costs, and social services would only have accentuated the cost-savings and quality-of-life benefits of our testing strategy. Future studies should seek to incorporate societal costs into their analyses. As per the recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine (41), we have developed an impact inventory to clarify the scope of this study (Supplementary Table 10).

In the current insurance environment, coverage for MODY genetic testing is often delayed or denied, as population-wide genetic testing is deemed cost prohibitive. However, our study shows that the addition of biomarker screening to identify an appropriate population for genetic testing made testing for MODY in U.S. pediatric patients with diabetes a cost-saving measure. Adding cascade genetic testing further increased QALY and decreased costs associated with the genetic testing strategy. Thus, this work presents a rare application of precision medicine that, if implemented now at the policy level, could reduce

health care costs and improve the lives of patients living with MODY.

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